REMARKS

The specification has been amended to include section headings as suggested by the examiner. Following the section headings "SUMMARY OF THE INVENTION" and "BRIEF DESCRIPTION OF THE DRAWINGS" appropriate paragraphs were included. These paragraphs are found in the specification as originally filed and are replicated merely for purposes of clarity. (*See*, page 1, lines 4-9 and page 8, lines 3-20, respectively.)

Claims 1, 6, 9, and 10 have been amended to recite "oxaliplatin." Support for these amendments can be found throughout the specification including, for example, page 1, lines 4-9; page 3, line 1 - page 5, line 9; page 5, lines 15-32; and page 7, line 1 - 20; in the Examples (page 8, line 23 - page 13, line 26); and in original claims 3 and 8.

Claims 3 and 8 have been canceled without prejudice.

Claim 4 has been amended to delete "chloride." Support for this amendment can be found throughout the specification including, for example, page 5, line 34 - page 6, line 1 and page 7, lines 1-5 and 14-25. (*See In re Johnson*, 558 F.2d 1008, 1019 (C.C.P.A. 1977) (The Court of Customs and Patent Appeals held that an amendment removing from the original claims two species satisfies *§ 112*, first paragraph, based on the disclosure in the specification of the those two species.)

Claim 5 has been amended to recite that concentrations of the cations of calcium and magnesium salts are "expressed as calcium or magnesium ions, respectively" to correct an obvious typographical error and to provide clarity. This amendment does not change the scope of the claim in any way.

Claim 6 has also be amended to replace "preventing" with "inhibiting." Support for this amendment can be found throughout the specification including, for example, page 1, lines 4-9; page 3, lines 1-3; page 5, lines 11-13; page 7, lines

1-6 and 14-25; and page 8, lines 13-20 (Figure 3); and in the Examples (page 8, line 23 - page 13, line 26).

Claim 13 has been added. Support for this claim can be found throughout the specification including, for example, page 7, lines 8-12.

Applicants submit that no new matter has been added via these amendments to the claims.

Objection to the Specification

The examiner objected to the specification because the specification did not include all sections listed in 37 C.F.R. § 1.77(b) with appropriate section headings. (Paper No. 20080128 at 5.) In the view of the Patent Office, "none of the section headings or a disclosure of joint research agreements or a cross-reference to related applications are present." (*Id.*) The examiner then require "[a]ppropriate action." (*Id.*)

The specification has been amended to include the suggested section headings, and where appropriate, to indicate that the section is "Not Applicable." Accordingly, the objection to the specification has been rendered moot and withdrawal is requested.

35 U.S.C. § 112, First Paragraph

Claims 1, 3-6, and 8-12[1] were rejected under § 112, first paragraph, as containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors, at the time that the application was filed, had possession of the claimed invention. (Paper No. 20080128 at 6.) The Office has taken the position that "[t]he specification fails to provide adequate written description for the describing the use of both an injectable and an oral form of calcium. Nowhere in Applicants' instant specification is there any

[1] Claims 3 and 8 have been canceled without prejudice. Accordingly, all rejections of these claims are moot and should be withdrawn.

written description showing examples, or incorporated by reference as prior art, calcium used in both dosage forms simultaneously, sequentially or separately." (*Id.* (emphasis original).)

The examiner then states that "it is imperative that an adequate written description is provided in the form of written examples, scholarly discussion or prior art incorporated by reference." (*Id.*, at 7.) The examiner then concludes that "[a]pplicants have provided none of these exemplifications; therefore the instant specification lacks adequate written description for the administration of calcium in an oral and a parenteral dosage at any time." (*Id.*)

Applicants respectfully traverse this rejection.

There is a strong presumption that an adequate written description of the claimed invention is present in an application as filed. *See In re Werthheim*, 191 USPQ 90, 97 (CCPA 1976); and M.P.E.P. § 2163(I)(A) (8 ed., Rev. 6, September 2007, p. 2100-174). Further, an applicant may show possession of the claimed invention by describing it using any descriptive means including, for example, words, structures, figures, diagrams and formulas. *See* M.P.E.P. § 2163(I) (8 ed., Rev. 6, September 2007, p. 2100-173).

It was the Patent Office's burden to clearly articulate evidence showing that the specification lacks a description that conveys to one skilled in the relevant art that the inventors, at the time that the application was filed, had possession of the claimed invention. The rejection simply does not meet this burden.

The examiner instead articulated a written description standard that cannot be found in the statute or precedent and is simply not the law. The examiner based the rejection on a determination "that an adequate written description is provided in the form of ***written examples, scholarly discussion or prior***

art incorporated by reference." (Paper No. 20080128 at 6 (emphasis added).) Contrary to the examiner's position, an applicant may show "possession of the claimed invention by describing the claimed invention with all its limitations using such descriptive means as words, structures, figures, diagrams and formulas . . . ." *See* M.P.E.P. § 2163(I)

Because the rejection employs an erroneous standard, the rejection cannot provide a *prima facie* case of obviousness. For this reason alone, the rejection is infirm and withdrawal is requested.

Moreover, even if the examiner had employed the correct legal standard, it is clear that the specification as filed satisfies the written description requirement. The specification includes various recitations of the use of calcium by both parenteral and oral routes.

> In an advantageous embodiment of the invention, ***part of the calcium is in injectable form and the other part is in oral form.***

Page 5, lines 26-28 (emphasis added).

> The concentrations of calcium and magnesium salts are chosen so as to allow intravenous administration of 2 to 3 g/day of said salts during the administration of oxaliplatin. The calcium concentrations are chosen so as to allow administration of 1 to 2 g/day *per os* during the eight days which follow.

Page 6, lines 10-15. ("*Per os*" is Latin for "by mouth.")

> The expression injectable form is understood to mean, for the purposes of the present invention, any liquid form capable of transporting the composition into the human body of a patient, such as for example isotonic solutions.
>
> The expression oral form is understood to mean any form suitable for oral administration, in particular tablets, capsules and solutions.

Page 6, lines 29-37

> The calcium and the magnesium may be used at any

> effective concentration which makes it possible to increase oxaliplatin tolerance; infusion in serum at 5% glucose containing 1 g of calcium gluconate and 1 g of magnesium sulfate before and after oxaliplatin gives good results.
>
> The administration of calcium by the oral route may also be carried out at any dose which makes it possible to obtain the desired effect, in particular at a dose of 1 g/day by the oral route for the 8 days which follow the treatment with oxaliplatin.

Page 7, lines 1-12.

> In some cases, it is found to be necessary to continue with the administration of Ca in order to reduce the risk of onset of neurological manifestations at a distance from the administration of oxaliplatin. In these cases, calcium, by the oral route, is effective and makes it possible to preserve the quality of life of the patients.

Page 11, lines 8-14 (Examples).

Thus, the specification describes the use of both an injectable and an oral form of calcium. In addition, the specification describes dosage forms, dosage amounts, dosage concentrations, and dosing regimens for injectable and oral administration of calcium.

In sum, the specification provides a detailed description of the use of both an injectable form and an oral form of calcium that far surpasses the disclosure required to satisfy the written description requirement. Accordingly, one skilled in the relevant art would readily recognize that the Applicants were, at the time that the application was filed, in possession of the claimed invention. Nothing more is required. For this additional reason, the rejection is deficient and withdrawal is requested.

Claims 1, 3-6, and 8-12 were rejected under 35 U.S.C. § 112 for lack of enablement. (Paper No. 20080128 at 7.) Applicants respectfully traverse this rejection.

The test for enablement is whether the specification contains disclosure sufficient to enable one of skill in the art to make and use the claimed invention without undue experimentation. M.P.E.P. § 2164.01 (8 ed., Rev. 6, September 2007, p. 2100-193). Moreover, it is the examiner's burden to demonstrate that a specification is not sufficiently enabling. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). As is well accepted, even a "considerable amount" of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance. M.P.E.P. § 2164.06 (8 ed., Rev. 6, September 2007, p. 2100-201) and *In re Wands*, 8 USPQ at 1404.

The examiner determined that:

> Applicant would need to show evidence that the oral dosage would have the desired physiological response through examples or scholarly discussion showing the nexus between what is commonly known in the art and that which Applicant asserts is his invention. In this particular case, ***the oral calcium dosage, in the salt forms outlined by Applicant in the instant specification, is required to be assessed for physiological activity by in vivo screening to determine if the oral dosage exhibits the desired pharmacological activity of treating or preventing neurotoxicity.*** Of the three studies disclosed by applicant in the instant specification on pages 9-11, none of the subjects were given an oral dose of any calcium salt at any time. Furthermore, all three studies only show that the regular infusion of calcium and magnesium are required to alleviate the onset of neurotoxicity which is readily known in the art. ***No studies were conducted with oral calcium and no drug treatment regimens comprising administering compositions of oxaliplatin, injectable magnesium and calcium and an oral form of calcium have been disclosed.*** (underline original, other emphasis added.)

(Paper No. 20080128 at 10 (underlining original; other emphasis added).) The examiner's determination appears to be based on two grounds.

First, examiner concluded that the present invention is not enabled because no working examples have been disclosed in the specification. (*Id.*) The mere absence of a working example, however, cannot alone support a determination of lack of enablement. In fact, it is not necessary that the invention even be reduced to practice before the date of filing of the application:

> ***An applicant need not have actually reduced the invention to practice prior to filing.*** In *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987), as of Gould's filing date, no person had built a light amplifier or measured a population inversion in a gas discharge. The Court held that "***The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it.***" 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)).
>
> ***The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation.*** *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

M.P.E.P. § 2164.02 (8 ed., Rev. 6, September 2007, p. 2100-196) (emphasis added).

The second ground upon which the examiner appears to support the rejection is that the specification discloses "no drug treatment regimens comprising administering compositions of oxaliplatin, injectable magnesium and calcium and an oral form of calcium have been disclosed." (*Id.*) As to this ground it appears that the examiner has not considered the specification as a whole. As discussed above, the specification includes various recitations of the use of calcium by both parenteral and oral routes.

> The concentrations of calcium and magnesium salts are chosen so as to allow intravenous administration of 2 to 3 g/day of said salts during the administration of

> oxaliplatin. The calcium concentrations are chosen so as to allow administration of 1 to 2 g/day *per os* during the eight days which follow.

Page 6, lines 10-15. ("*Per os*" is Latin for "by mouth.")

> The calcium and the magnesium may be used at any effective concentration which makes it possible to increase oxaliplatin tolerance; infusion in serum at 5% glucose containing 1 g of calcium gluconate and 1 g of magnesium sulfate before and after oxaliplatin gives good results.
>
> The administration of calcium by the oral route may also be carried out at any dose which makes it possible to obtain the desired effect, in particular at a dose of 1 g/day by the oral route for the 8 days which follow the treatment with oxaliplatin.

Page 7, lines 1-12. In particular, the examples disclose that:

> [i]n some cases, it is found to be necessary to continue with the administration of Ca in order to reduce the risk of onset of neurological manifestations at a distance from the administration of oxaliplatin. ***In these cases, calcium, by the oral route, is effective*** and makes it possible to preserve the quality of life of the patients.

Page 11, lines 8-14 (Examples) (emphasis added).

Thus, contrary to the examiner's position, the specification describes not just the use of both an injectable and an oral form of calcium, but also dosage forms, dosage amounts, dosage concentrations, and dosing regimens for injectable and oral administration of calcium.

The examiner also objects to the use of the phrase "to prevent." (Paper No. 20080128 at 11.) Claim 6 was the only claim that recited any variation of the word "prevent." Claim 6 has been amended to replace the word "preventing" with "inhibiting."

In light of the forgoing, the specification provides ample guidance to one of skill in the art to make and use the claimed invention without undue experimentation. Nothing more

is required to satisfy he enablement requirement. Accordingly, withdrawal of the rejection is requested.

35 U.S.C. § 112, Second Paragraph

Claim 5 has been rejected as indefinite because, in the view of the Patent Office, the "phrase, 'the concentrations being expressed as calcium ion,' in lines 6-7 . . . is confusing due to the preceding statement referring to the calcium and magnesium concentrations." (Paper No. 20080128 at 7.) As suggested by the examiner, claim 5 has been amended to recite "the concentrations being expressed as calcium or magnesium ions, respectively." In addition, the claim has been amended to make clear that it is the concentration of the cation of each salt that is being recited. Accordingly, the rejection has been rendered moot and withdrawal is requested.

35 U.S.C. § 103(a)

Claims 1, 3-6, and 9-12 have been rejected under 35 U.S.C. § 103(a) as unpatentable over *Lainé-Cessac et al., Acute Oxaliplatin Neurotoxicity Dramatically Improved with Intravenous Calcium and Magnesium Salts*, Therapie, Vol. 53, p. 183 (1998) ("*Lainé-Cessac*") in view of Chazard, U.S. Patent Application 2002/0045632 ("*Chazard*"). (Paper No. 20080128 at 15.)

In the view of the Patent Office, *Lainé-Cessac* discloses that "oxaliplatin-induced neurotoxicity (1st sentence) can be dramatically improved after simultaneous (patient F/49 in table - given 4 minutes after the start of the 2-hour infusion of oxaliplatin) or postinjection (patient F/59 in table-given 15 minutes after the end of the infusion) administration of calcium and magnesium." (*Id.*) The Patent Office has acknowledged, however, that *Lainé-Cessac* differs from the claimed invention in that it does not disclose "the use of an oral calcium formulation nor the administration dosages or schedules." (*Id.*, at 7.)

To fill the acknowledged gap, the Patent Office relies on *Chazard* as disclosing "the use of an oral formulation of calcium folinate and an intravenous administration oxaliplatin (paragraph 36) to treat tumors (Abstract)." (*Id.*) The Patent Office then determined that:

> It would have been obvious to one of ordinary skill in the art, in view of the teachings of Laine-Cessac et al., drawn to a parenteral composition comprising a parenteral drug regimen of oxaliplatin and magnesium and calcium salts in the treatment of adenocarcinoma, and Chazard, drawn to an oral formulation of calcium folinate and an intravenous administration oxaliplatin to treat tumors, a preparation of all of the elements of both formulations would similarly be useful in treating tumors and alleviating neuropathy. . . . Therefore, combining the teachings of Laine-Cessac et al. and Chazard would have resulted in a drug regimen for the treatment of cancer that contained an oral calcium dosage, a parenteral dosage of calcium and 'magnesium and an active ingredient which releases oxalate during its metabolism (e.g., oxaliplatin).

(*Id.*, at 16.) Applicants respectfully traverse.

Lainé-Cessac discloses that the acute neurotoxic effects of oxaliplatin administration can be dramatically improved by intravenous administration of calcium gluconate and magnesium sulfate immediately after onset of the neurotoxic effects. *Lainé-Cessac* is silent as to oral administration of calcium.

Chazard discloses "[o]ral dosage form for administration of the combination of tegafur, uracil, folinic acid, and oxaliplatin and method of using the same." (Title.) In fact, *Chazard* is directed specifically to an oral dosage as an improvement upon an injectable form of it compositions:

> It has been observed that 5-fluorouracil can enhance the activity of oxaliplatin. However, because 5-fluorouracil cannot be administered orally, the mode of administration for this combination therapy requires a more invasive form of administration such as by

> intravenous injection, and therefore typically requires administration by trained medical personnel.
>
> ***It would be an advance*** in the art of treating tumors, especially colorectal cancerous tumors, ***if a therapy could be developed employing a potentiated form of oxaliplatin through the action of 5-fluorouracil in a convenient dosage form for oral administration***.

(¶¶ 0007-0008 (emphasis added).)

Chazard discloses that "5-fluorouracil cannot be administered orally." (¶ 0003.) *Chazard* discloses, however, that "the combination of tegafur and uracil in amounts sufficient to convert tegafur to 5-fluorouracil (preferably a molar ratio of about 1:4) can be administered orally. It was unexpectedly discovered that oral administration of this combination produced sufficient 5-fluorouracil that potentiation of oxaliplatin would take place despite the inability of 5-fluorouracil itself to be effectively administered orally." (¶ 0015.) In sum, *Chazard* explicitly discloses that oral administration of its compounds is absolutely critical to the invention:

> The ***oral dosage form*** used in the present invention ***provides significant advantages*** over administering the combination by other modes of administration which are more invasive. In the treatment of tumors, a potential ***reduction in the cost of therapy*** because skilled medical personnel are not required to administer the drug and the ***psychological benefits afforded a patient*** by taking an oral medication provide significant benefits for patient care.

(¶ 0016 (emphasis).)

Thus, any combination of *Lainé-Cessac* and *Chazard* that results in the claimed invention must necessarily include a composition including injectable magnesium and injectable calcium or a method including injection of magnesium and calcium. Such a composition or method destroys the operability of *Chazard*, *i.e.*, a composition or method requires an injection

that 1) increases the cost of therapy and 2) removes the psychological benefits afforded a patient by taking an oral medication. However, a modification of references that destroys the operability of the references is not obvious. *See, In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) (reversing the decision of obviousness on the ground that the proposed modification of the prior art would have rendered the claimed invention inoperable for its intended purpose). For this reason alone, the rejection fails to present a *prima facie* case for obviousness and withdrawal is requested.

Moreover, *Chazard* includes calcium only as the counter-ion to the folinic acid, which is the active ingredient. *Chazard*, does not disclose that calcium has any activity of its own. The compositions of *Chazard* are directed to only potentiating or enhancing the effect of oxaliplatin:

> The present invention is directed to a dosage form suitable for oral administration to a mammal for the treatment of tumors, especially colorectal tumors, that exhibits a synergistically enhanced effect in combination with oxaliplatin. In particular, there is provided in accordance with the present invention a dosage form suitable for oral administration to a mammal having a tumor comprising an effective amount of each of tegafur, uracil, and folinic acid or a pharmaceutically acceptable salt thereof to a patient undergoing treatment with oxaliplatin, wherein said dosage form is a potentiator of oxaliplatin.

(¶ 0009.)

Contrary to the examiner's position, none of the examples of *Chazard* disclose any reduction in oxaliplatin-mediated toxicity. The examiner points to a statement in Example 2 that "[e]ntry criteria for the study included . . . no evidence of peripheral neuropathy . . . ." (Paper No. 20080128 at 16, *citing Chazard*, ¶ 0034.) This statement, however, is an merely explanation of the criteria for

selecting study subjects, not a description of any endpoint measured in the study.

Example 2 is actually directed only to determining the maximum tolerated dose:

> The study continued to each progressive level until the maximum tolerated dose (MTD) was experienced. The MTD was defined as the dose level at which three or less patients out of six in a cohort experienced no dose limiting toxicity (DLT) at that cycle of treatment.

(¶ 0037.) *Chazard* concludes that of the 19 patients treated with its compositions up to maximum does, none have exhibited dose limiting toxicity. (*See* ¶ 0038.) This study does not disclose or suggest that there is no toxicity, only that the exhibited toxicity was not severe enough to warrant stopping the treatment. In fact, on average each of the 13 patients evaluated for treatment efficacy experienced twelve events of neurotoxicity with a cumulative dose of 705 mg/m^2 of oxaliplatin delivered over the course of six days. (*See* ¶ 0035 (Table) and ¶ 0040 (Table) (each patient suffered nine events of Grade I parasthesia and three events of Grade II parasthesia).)

However, such levels of toxicity are typical of oxaliplatin-mediated neurotoxicity. For example, a recent article shows that "[o]xaliplatin-induced cumulative neurotoxicity develops progressively" and that of 187 patients treated with oxaliplatin, 72 showed Grade I neurotoxicity, 56 showed Grade II neurotoxicity, and 33 showed Grade III neurotoxicity. Matsusaka *et al.*, *Measures of oxaliplatin-induced neurotoxicity in 187 patients with FOLFOX4*, J Clin. Oncol., 25:185 p. 14552 (2007) (attached as Exhibit A.). *Matsusaka* states that the "median cumulative does of oxaliplatin were 170 mg/m^2 [in those suffering Grade I neurotoxicity and] 845.8 mg/m^2 [in those suffering Grade II neurotoxicity]."

Chazard discloses that its subjects suffered Grade II neurotoxicity at a cumulative dose of oxaliplatin less than the

mean cumulative does expected to produce such a result, *i.e.* 705 mg/m^2 v. 845.8 mg/m^2). In sum, there is nothing in *Chazard* that teaches or suggests that its compositions produce any reduction of oxaliplatin-mediated neurotoxicity. In fact, *Chazard* discloses that its compositions produce a greater prevalence of neurotoxicity at a lower dose of oxaliplatin.

Thus, the combination of *Lainé-Cessac* and *Chazard* would, based on the disclosure of *Chazard*, result in a composition and method that increases neurotoxicity. Such a composition or method destroys the operability of *Lainé-Cessac*, which is directed to reduction of acute oxaliplatin-mediated neurotoxicity. As discussed above, a modification of references that destroys the operability of the references is not obvious. *See, In re Gordon*, 733 F.2d at 902. For this additional reason, the rejection fails to present a *prima facie* case for obviousness and withdrawal is requested.

As discussed in the Applicants' previous response (November 28, 2007), the claimed invention is also nonobvious because it solves a problem that the prior art did not recognize. This argument stands unrebutted by the present Office Action and is re-presented here for completeness.

Before the present Applicants' invention, it was believed that the neurotoxic effects of oxaliplatin appeared only during or immediately after infusion of the oxaliplatin. In other words, the late-onset of neurotoxic effects was not a concern. Consequently, and as borne out by the cited prior art itself, therapies for treating these neurotoxic effects focused exclusively on immediate treatment. *See, e.g., Lainé-Cessac.* However, this belief turned out to be mistaken. As Applicants explained in paragraph [0053] of the present specification, "[i]n some cases, it is found necessary to continue with the administration of Ca in order to reduce the risk of ***onset of neurological manifestations at a distance from***

the administration of oxaliplatin." (Emphasis added.) In solving this problem with a combination of injectable and oral administration of calcium, Applicants' claimed invention thus produces unexpected results in treating the previously unappreciated late-onset neurological side effects of oxaliplatin.

Inventions based on application of known solutions to previously unknown problems have been held to be non-obvious and patentable. In *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923), the Supreme Court ruled that the first recognition of the existence of a problem is not obvious and involves discovery and invention. In *Eibel Process*, the patent in question was directed to an improvement in a standard paper making machine. In the machine, a stream of pulp stock flowed onto a moving wire cloth in order to drain water out of the stock over the 30 foot-length of the cloth. The prior art taught that increasing the speed of the wire cloth increased productivity, but at the same time, caused the defective paper with poor quality. The patentee's contribution was to increase the pitch of the wire cloth in order to use gravity to increase the rate of flow of pulp on the wire cloth to equal the rate of flow of the wire cloth itself. The Supreme Court held thusly:

> It was the discovery of the source not before known and application of the remedy for which *Eibel* was entitled to be rewarded in his Patent. . . . We cannot agree with the Circuit Court of Appeals that the causal connection between the unequal speeds of the stock and the wire, and the disturbance and rippling of the stock, and between the latter and the defective quality of the paper in high speeds of the machine was so obvious that perception of it did not involve discovery which will support a patent.

Eibel Process, at 68.

Similarly, in *In re Nomiya*, 509 F.2d 566, 184 USPQ 607 (C.C.P.A. 1975), the Court of Customs and Patent Appeals (CCPA) held that the doctrine established by the Supreme Court in *Eibel Process* also applies when the inventor was the first to encounter or perceive a problem even though he uses known or obvious means of solving it. *Nomiya* dealt with an improvement in an insulated gate-type field effect transistor (IGFET) for use as a switching device in memory circuits having very low capacitance. The CCPA reasoned thusly:

> If, as appellants claim, there is no evidence of record that a person of ordinary skill in the art at the time of appellants' invention would have expected the problem in the IGFET to exist at all, it is not proper to conclude that the invention which solves this problem, which is claimed as an improvement of the device, would have been obvious to that hypothetical person of ordinary skill in the art. The significance of evidence that a problem was known in the art is, of course, that knowledge of a problem provides a reason or motivation for workers in the art to apply their skill to its solution. Logically, the instant situation is one step removed from the circumstances illustrated by *Eibel Process Co. v. Minnesota & Ontario Paper Co.* ... where *the problem* of rippling in paper produced on Fourdrinier paper-making machines at high speed *was known*, but the source of the problem was not.

Nomiya, 509 F.2d at 572, 184 USPQ at 612-613.

For this additional reason, the rejection fails to present a *prima facie* case for obviousness. Accordingly, withdrawal of the rejection is requested.

As it is believed that all of the objections and rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: June 9, 2008

Respectfully submitted,

By _____

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EXHIBIT A

Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings (Post-Meeting Edition).
Vol 25, No 18S (June 20 Supplement), 2007: 14552

Abstract

Measures of oxaliplatin-induced neutrotoxicity in 187 patients with FOLFOX4

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14552

Background: Oxaliplatin-based regimen (FOLFOX regimen) for patients with colorectal cancer have improved survival. Neurotoxicity is the most frequent dose-limiting toxicity of oxaliplatin. Various strategies and pharmacologic agents are currently under investigation to prevent or treat oxaliplatin-induced neurotoxicity. One of them is Stop-and-Go strategy based on the observation of reversibility of the neurotoxic symptoms after discontinuation of oxaliplatin. Stop-and-Go concept will prolong the time of oxaliplatin-based therapy as long as antitumor efficacy is still maintained. **Methods:** Patients with a histologically verified advanced colorectal carcinoma were eligible for the study. From April 2005 to March 2006 at Cancer Institute Hospital, 187 patients whom treated with bimonthly oxaliplatin-based regimen (FOLFOX4) were enrolled. An oxaliplatin specific neurotoxicity scale are distinct from the National Cancer Institute common toxicity criteria classification (CTC-AE vol. 3). This study was performed to carefully assess the onset and duration to recovery of oxaliplatin neurotoxicity and resumption rate of FOLFOX4. **Results:** Neurotoxicity was observed in 72 patients with Grade 1, 56 patients with Grade 2 and 33 patients with Grade 3. Oxaliplatin-induced cumulative neurotoxicity develops progressively. The median cumulative doses of oxaliplatin were 170 mg/m^2 with Gr. 1; 845.8 mg/m^2 with Gr. 2; and 850 mg/m^2 with Gr. 3. The median time to onset were 16 days with Gr. 1; 174 days with Gr. 2; and 177 days with Gr. 3. The median time to recovery after stopping the therapy and the median time to progression during the discontinuation of oxaliplatin were 56 and 59 days, respectively, in patients allocated to Gr. 2 compared with 106 and 73 days, respectively, in patients allocated to Gr. 3. The recovery time during the discontinuation showed a statistically significant reduction of the values in the Gr. 2 but not in Gr. 3 ($p = 0.0024$). The resumption rates of oxaliplatin were 73.7% with Gr. 2 and 46.4% with Gr. 3. **Conclusions:** Our results may focus to manage time course of Stop-and-Go strategy in clinical practice.

No significant financial relationships to disclose.